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Original Article

Ultrasound and Color Doppler Evaluation of Axillary Lymph Nodes in Breast Carcinoma with Histopathological Correlation

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Abstract

Introduction: Accurate assessment of the axillary lymph node status and identifying metastatic changes is extremely important in the management of breast cancer.

Aims and Objectives: The aims of this study are to assess the role of ultrasound and color Doppler in diagnosing metastasis to axillary lymph nodes in patients with breast cancer and to correlate with histopathological findings.

Materials and Methods: In this prospective study, 62 female patients of biopsy-proven breast cancer were evaluated by high-resolution ultrasonography (USG) and color Doppler in the Department of Radiodiagnosis, NSCB Medical College, Jabalpur, from March 2016 to March 2017, with 5–10 MHz linear transducer. Lymph nodes were assessed using gray-scale and color Doppler parameters such as nodal size, shape, L/S ratio, border, hilum, echotexture, necrosis, matting, and angioarchitecture. A provisional diagnosis was suggested after the ultrasound examination, and these findings were correlated with the tissue diagnosis obtained on subsequent axillary dissection specimen.

Results: In our study of 62 cases, 39 patients had metastasis in axillary lymph nodes. Lymph node with oval shape (L/S ratio >2), echogenic hilum, homogenous echotexture, and hilar vascularity was considered as significant parameters in detecting non-metastatic (reactive) lymph nodes. Lymph nodes number ≥3, long axis/short axis ratio <1.4, resistivity index >0.7, pulsatility index >1.4, and non-hilar cortical blood flow were most reliable parameters for diagnosing metastatic lymph nodes with a diagnostic accuracy of 75.80%, 69.35%, 79%, 72.58%, and 85.48%, respectively.

Conclusion: This study concludes that USG examination proved as a valuable primary investigation to identify lymph nodes and differentiate non-metastatic and metastatic lymphadenopathy.

Key words: Axillary lymphadenopathy, Breast cancer, Color Doppler, Ultrasound

INTRODUCTION

Axillary lymph node metastases have been one of the most important prognostic parameters in patients with breast cancer. Differentiation between metastatic and non-metastatic axillary lymph nodes is extremely important at the earliest because a delayed diagnosis can lead to upstaging of the disease making a curable lesion incurable.

The sentinel lymph node is the first lymph node to receive lymph drainage from the primary tumor and is also highly predictive for the status of the remaining axillary lymph nodes. But as, the sentinel lymph node biopsy (SLNB) has not found wide acceptance in developing countries due to the requirement of nuclear medicine, frozen section facilities, waiting intraoperatively for frozen section reports, thus prolonging operating time, post-procedure complications (upper limb lymphedema, arm paresthesia,

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chronic pain, and immobility), and a 5–10% false-negative rate.[1] Therefore, it will be advantageous to evaluate the efficacy of noninvasive procedure such as ultrasonography (USG) and color Doppler in differentiating metastatic from non-metastatic nodes in biopsy-proven breast carcinomas.

Thus, the aim of our study was to use ultrasound and color Doppler imaging for the pre-operative evaluation of axilla in breast cancer and to correlate the findings with the tissue diagnosis obtained on subsequent axillary dissection specimen. The goal was to identify the subset of patients who could be reliably diagnosed on the basis of USG and color Doppler to harbor axillary nodal metastasis. Such patients could be spared a SLNB procedure and offered axillary lymph node dissection (ALND) upfront.

MATERIALS AND METHODS

The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all 62 female patients who were referred for USG of breast and axilla to the Department of Radiodiagnosis, NSCB Medical College, Jabalpur. The study was undertaken over 1 year from March 2016 to March 2017. All scans carried out on 5–10 MHz linear transducer using Siemens Acuson ×300, Sonoscape SS1600, Philips HD 7XE machine.

Inclusion Criteria

1. Female patients of all age groups with biopsy positive breast carcinoma were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Post-operative patients, patients on chemotherapy or radiotherapy, and those with prior axillary intervention.
2. Patients with no evidence of axillary lymphadenopathy on ultrasound.

The patients were examined in the supine position with the arm in 90° abduction and external rotation. In this position, the axillary vessels have a nearly straight course facilitating orientation and all parts of axilla could be thoroughly examined.

Color Doppler USG was also performed with low-velocity parameter settings and high gain using a slow scanning technique. Sample volume was adjusted to the vessel size and was centered in the vessel, and the angle of insonation was kept at 60° or less in all examinations. Doppler spectral waveforms were recorded from different vessels whenever possible for each node, and the highest value was selected. Spectral Doppler analysis was performed on the vessel with the most rigorous flow, and the peak systolic velocity, pulsatility index (PI), and resistive index were recorded.

The Axillary Lymph Nodes were Examined Under the Following Headings

Gray-scale USG

- Number of lymph nodes detected by USG
- Size of the largest lymph node
- Shape
- Long-to-short axis (L/S) ratio
- Echogenicity of the hilum
- H/L ratio (long axis of hilum/long axis of lymph node)
- Other ancillary morphlogical changes (necrosis, calcification, and matting of lymph nodes).

Color Doppler USG

- Vessel location
- Flow pattern
- Resistivity index (RI): Peak systolic velocity - end diastolic velocity/peak systolic velocity
- PI: Peak systolic velocity - end diastolic velocity/mean velocity.

Lymph node metastasis was characterized by the following sonomorphological and color Doppler changes:

Gray-scale USG findings

- Increase in size (short axis diameter >7 mm)
- Increase in number (three or more than 3)
- Change in shape (from oval to more round in appearance-L/S ratio <2)
- Altered echotexture (cystic, necrotic inclusions, and disappearance of echogenic hilum)
- Eccentric asymmetric cortical thickening and focal cortical bulge due to subcortical metastatic deposits.

Color Doppler (CD) findings

- Metastatic nodes have a predominantly peripheral non-hilar blood flow pattern
- Pulse Doppler with spectral waveform pattern revealed sharp systolic peaks in metastatic nodes with high RI and PI values.

In Axilla with multiple nodes, the node with minimum L/S ratio and H/L ratio and maximum RI and PI were taken into account. Sensitivity and specificity of various ultrasound and color Doppler parameters were recorded in differentiating non-metastatic from metastatic lymph nodes. All patients underwent modified radical mastectomy. The mastectomy and axillary specimen were evaluated by conventional histopathology. The results of USG and CD ultrasound were correlated with the histopathology of the lymph nodes harvested in the axilla.

RESULTS

In our study, age range from 40 to 49 years had a highest proportion of cases as shown in Table 1. Of 62 patients

with lymph nodes detected on USG, 39 patients revealed metastasis on histopathological examination. Lymph nodes which were suspicious for metastasis had round shape (L/S ratio <2), distorted hilum, eccentric cortical thickening, focal cortical bulge, heterogenous echotexture, intranodal necrotic changes, multiple clumped nodes, peripheral non-hilar cortical or mixed vascularity pattern, and high RI (>0.7) and PI values (>1.4). Correlation of sonographic findings with histopathological findings was performed.

In our study, we observed that the cutoff value of 2 or less for L/S ratio yielded a sensitivity of 79.49% and specificity of 65.22% to detect metastasis [Table 2]. The number of cases with visible hilum on USG was 33. It was observed that H/L ratio ≤0.5 yielded a sensitivity of 90% and a specificity of 91.30% [Table 3].

On color Doppler studies, it was shown that exclusively peripheral non-hilar cortical vascular pattern showed the highest positive predictive value (PPV) of 100% to detect metastatic changes [Table 4]. In our study, we found that the cutoff value of 0.7 for RI yielded a sensitivity of 92.3% and specificity of 56.2% and cut off value of 1.4 for PI yielded a sensitivity of 82.5% and specificity of 65.2% for labeling lymph nodes positive for metastasis [Tables 5 and 6].

Table 1: Age distribution

Age groups (in years)	Number of cases
30–39	13
40–49	26
50–59	11
60–69	9
70–79	3

Table 2: Distribution of L/S ratio on USG with histopathological correlation

L/S ratio	Number of cases without metastasis	Number of cases with metastasis
≤2	8	31
>2	15	8

χ^2=12.39, *P*<0.001. USG: Ultrasonography

Table 3: Distribution of H/L ratio in cases with visible hilum on USG with histopathological correlation (number of patients=33)

H/L ratio	Number of cases without metastasis	Number of cases with metastasis
<0.5	2	9
>0.5	21	1

χ^2=20.73, *P*<0.001 H/L ratio=ratio of long axis of hilum to the long axis of lymph node. USG: Ultrasonography

DISCUSSION

USG is cost-effective, easily available, radiation-free, non-invasive, safe and is a primary investigation in detection of axillary lymph nodes in breast malignancies. Thus, our study confirmed the reliability of ultrasound parameters to detect metastasis.

Size

Nodes with short axis diameters less than the cutoff (0.7 cm) point were considered non-metastatic and those with >0.7 cm had the sensitivity of 94.8%, specificity of 52.17%, PPV of 77.08%, negative predictive value (NPV) of 85.7%, and diagnostic accuracy of 79.03% in diagnosing metastasis to the axillary lymph nodes.

Size alone cannot be as used relevant criteria, as metastatic nodes may be small and acute inflammatory or reactive nodes, quite large. It has been shown that the size of the lymph nodes is not an accurate predictor of metastasis, this implies its poor specificity.

Shape

In our study of 62 patients, 21 had round appearance of axillary lymph nodes, in which 19 cases were positive for nodal metastasis. Benign nodes are oval or elongated

Table 4: Distribution of vascular pattern of axillary lymph node with histopathological correlation

Vascular pattern	Total	Number of cases without metastasis	Number of cases with metastasis	PPV (%)
Hilar	21	20	1	4.76
Central perihilar	9	2	7	77.77
Peripheral non-hilar	28	0	28	100
Mixed	4	1	3	75

PPV: Positive predictive value

Table 5: Distribution of RI on color Doppler ultrasound with histopathological correlation

RI	Number of cases without metastatic lymph nodes	Number of cases with metastatic lymph nodes
<0.7	13	3
>0.7	10	36

χ^2=18.01, *P*<0.001, RI: Resistivity index

Table 6: Distribution of PI on color Doppler ultrasound with histopathological correlation

PI	Number of cases with non-metastatic lymph nodes	Number of cases with metastatic lymph nodes
<1.4	15	7
≥1.4	8	32

χ^2=14.12, *P*<0.001, PI: Pulsatility index

[Figure 1] while malignant nodes are often described as rounded [Figure 2]. This is better described in terms of L/S ratio, i.e., the ratio between the longitudinal axis (L) of the node and the nodal transverse or short axis (S), diameter, which is used to define the nodal shape. The long axis of an oval benign node will be at least 2 times greater than the axial diameter, which is described as L/S >2 or S/L <0.5. In malignant rounded nodes, the value of L/S is <2 or even <1.4.

In our study, using a longitudinal-transverse axis, ratio of 2 or lower resulted in a sensitivity of 79.49% and a specificity of 65.22% in differentiating benign from metastatic nodes.

According to the studies done by Yang and Metreweli[2] using a longitudinal-transverse axis, ratio of 2 or lower resulted in a sensitivity of 67% and a specificity of 71% in differentiating benign from malignant nodes.

Hilum

Normal lymph nodes present a central echogenic hilum. This appearance is due to the abutment of multiple medullar sinuses acting as interfaces. The absence of an echogenic hilum due to replacement or effacement is considered to represent diagnostic criteria of abnormality and is significantly greater in malignancies than in benign lesions.

In our study of 62 patients, 29 had distorted echogenic hilum, which on histopathological examination revealed metastasis in all 29 patients, resulting in 100% PPV [Table 7], while 33 patients retained their hilar echogenicity (23 patients with maintained central echogenic hilum and 10 patients with displaced hilum). Among patients who had hilum present, 11 patients revealed H/L ratio equal to or <0.5. Among these 11 patients, 9 were diagnosed as having metastasis and rest 2 had benign nodes resulting in PPV of 81%.

H/L ratio ≤0.5 yielded a sensitivity of 90% and a specificity of 91.30% to detect nodal metastasis in known cases of breast malignancy. ($P < 0.001$ shows statistically significant association).

Table 7: PPV of the most reliable ultrasound parameters for evaluation of axillary lymph node metastasis

Ultrasound criteria for metastasis	Non-metastatic	Metastatic	PPV (%)
Round shape	1	20	95
Absent echogenic hilum	0	29	100
Eccentric cortical thickening	4	8	66.6
NHBF (in patients with only peripheral vascular pattern)	0	28	100

PPV: Positive predictive value, NHBF: Non Hilar blood flow

According to Dudea *et al.*,[3] the association of round shape and absent echogenic hilum, termed as a stringent criteria for malignancy, had high specificity.

Vanizi *et al.*[4] found H/L ratio <0.5 to be highly suspicious of malignant deposit. He also observed that H/L ratio of <0.30 was found to predict metastatic deposit in the node with a sensitivity of 81%, specificity of 83%, and a diagnostic accuracy of 82%.

Margins

Irregular or angular nodal margins represent a criterion of suspicion for metastasis which usually indicates invasive, extracapsular, and extranodal spread and bears a severe prognosis, while benign nodes are characterized by sharp margins. In our study, 34 patients had irregular nodal margins, of these lymph nodes of 32 patients revealed metastasis.

Number of Lymph Nodes

In our study, patients having axillary metastasis had the number of lymph nodes as diagnosed by ultrasound in the range from 2 to 6, mean 3 ± 0.82 ($P < 0.001$).

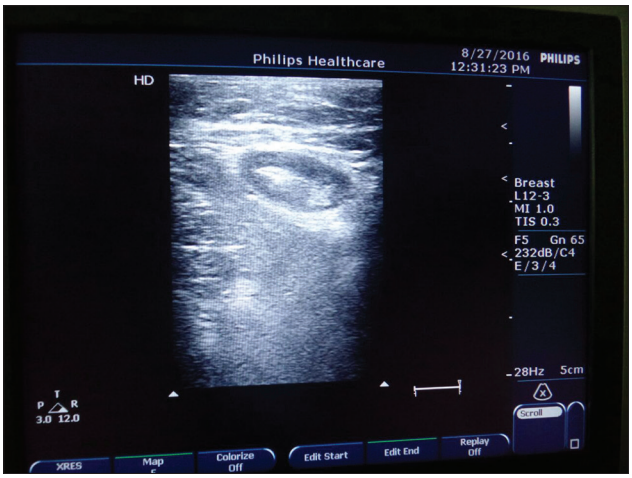

Figure 1: Ultrasonography image showing normal oval shape of axillary lymph node with maintained echogenic hilum

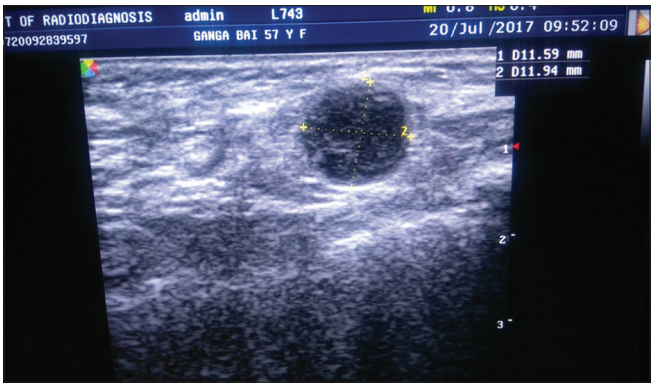

Figure 2: Ultrasonography image showing L/S ratio nearly 1, resulting in roundening of lymph node, suspicious of metastasis

Table 8: Accuracy of various ultrasound and color Doppler parameters for evaluation of metastasis in axillary lymph nodes

USG and CD parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Number of LNs 3 or more	74.36	78.26	85.29	64.29	75.80
Size (short axis diameter>0.7 cm)	94.8	52.17	77.08	85.7	79.03
L/S ratio (<2)	79.49	65.22	79.49	65.22	74.1
RI≥0.7)	92.31	56.52	78.26	81.25	79
PI (≥1.4)	82.5	65.22	80.00	68.18	75.80
Non-hilar blood flow	79.49	95.65	96.87	73.33	85.48

USG: Ultrasonography, CD: Color Doppler, PPV: Positive predictive value, NPV: Negative predictive value, RI: Resistivity index, PI: Pulsatility index

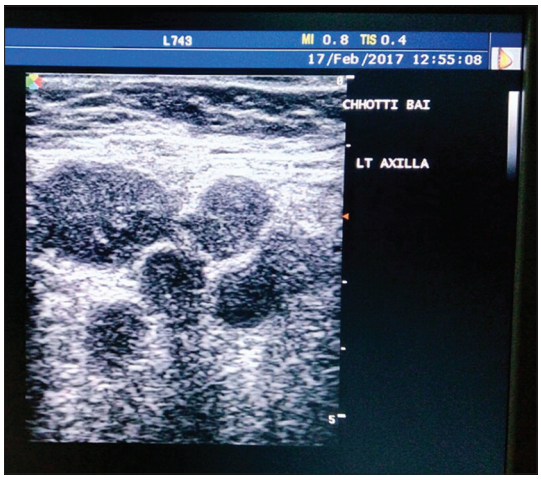

Figure 3: Ultrasonography image showing multiple axillary lymph nodes with loss of hilar echogenecity

Figure 4: Ultrasonography image showing eccentric cortical thickening (8 mm), suspicious of metastasis

A total of 34 patients were diagnosed with three or more than three axillary lymph nodes on USG [Figure 3]. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of multiple lymph nodes (three or more than three) in diagnosing nodal metastasis were 74.36%, 78.26%, 85.29%,64.29%, and 75.80%, respectively. In the study done by Das and Khanna,[5] the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of nodal metastasis

Figure 5: Ultrasonography image showing focal cortical bulge due to subcortical metastatic deposits

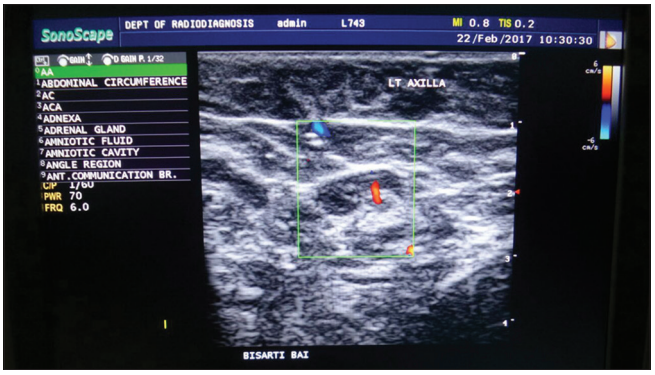

Figure 6: Ultrasonography image with color Doppler of axillary lymphnode showing central hilar vascularity pattern

in multiple lymph nodes (three or more than three) were 69%, 85%, 73%, 82% and 79%, respectively.

Structural Changes

Structural changes are, most often, encountered in malignant nodes and were absent in benign conditions.

Eccentric Cortical Thickening

In our study, lymph nodes of 12 patients had eccentric asymmetrical cortical thickening (>3 mm) [Figure 4], out of these lymph nodes of 8 patients were positive for metastasis. Focal cortical hyperplasia is indicative of partial tumor infiltration and represents a useful, sign for identifying metastatic nodes [Figure 5].

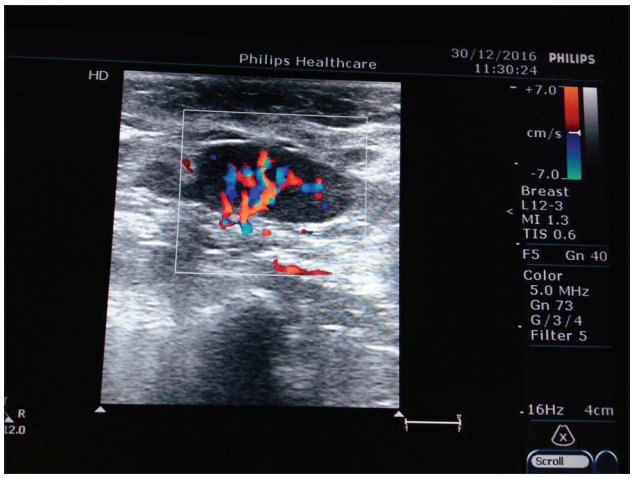

Figure 7: Ultrasonography image with color Doppler showing perihilar branching vascularity in axillary lymph node

Figure 8: Ultrasonography image with color doppler showing peripheral non-hilar cortical vascularity suggestive of metastatic changes

Figure 9: Ultrasound with color Doppler showing mixed vascularity (hilar+peripheral) of axillary lymph node

Intranodal Necrosis

In our study, two patients had intranodal necrosis, one was of coagulative type, and the other was associated with anechoic cystic changes. On histopathological examination,

Figure 10: Ultrasonography image showing pulsed Doppler spectral waveforms obtained from benign non-metastatic nodes with low resistivity index (0.48), low pulsatility index (0.62), and rounded systolic peaks

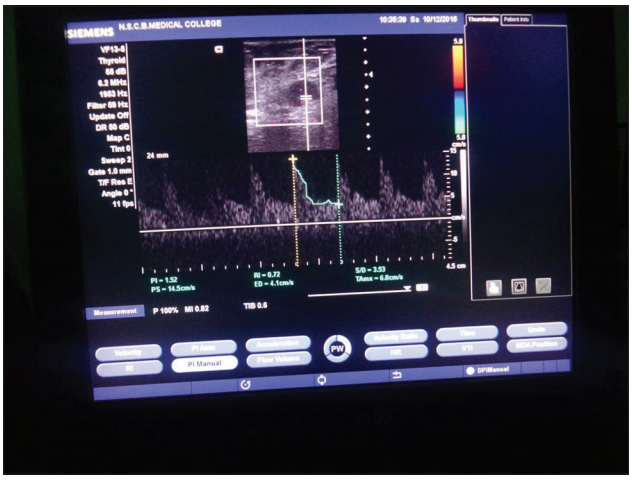

Figure 11: Ultrasonography image showing pulsed Doppler spectral waveforms obtained from metastasis-bearing lymph nodes with high resistivity index (0.72), high pulsatility index (1.52), and sharp systolic peaks

both were positive for nodal metastasis. Dudea *et al.*[3] described that intranodal necrosis indicates metastasis in most instances. It encompasses the coagulation or liquefaction type.

Coagulation necrosis appears as an echogenic focus that casts no shadow and shows no contact with the hilum or continuity with perinodal fat. Although necrotic changes are seen in metastasis, they are also seen in benign inflammatory nodes as well. Therefore, this type of necrosis represents a sign of certainty for pathologic changes, without disease specificity.

Cystic or liquefaction necrosis appears as anechoic areas within the structure of the lymph node. In patients with carcinoma, the presence of a cystic lymph node detected by USG is highly suggestive of locally metastatic disease However, the inflammatory nodes as may also present with non-malignant cystic necrosis.

Matted Lymph Nodes

In our study, 5 patients were diagnosed as having multiple coalesced matted lymph nodes. Moreover, all 5 had metastasis on histoplathological examination resulting in 100% PPV.

Matting of the lymph nodes is suggestive of metastasis. Dudea *et al.*[3] described that the presence of matting suggests extracapsular spread of malignancy. In his study, matting was encountered in 66% of cases with metastasis.

Color Doppler

Vessel location and flow pattern

Hilar vascular pattern

The hilar signal appears as Y-shaped or club-shaped color signals that occupy the central, hilar region of the lymph node. Inflamed or reactive lymph nodes tend to be fed by a single hilar artery [Figure 6]. In our study, of 62 patients, 21 patients had central hilar flow pattern which was fed by single vascular pedicle. Of these, only one patient had metastatic deposits.

Perihilar Vascular Pattern

It was defined as a simple hilar vessel signal with centrifugal branches oriented radially [Figure 7]. In our study, 9 patients had perihilar vascular pattern with multiple vascular pedicles in which 7 patients revealed metastasis.

Peripheral Non-hilar Vascular Pattern

It was defined as circumferential linear vascularity along the periphery of the node with no detectable connection to the hilum [Figure 8]. Metastases to lymph nodes stimulate the development of transcapsular tumor neovascularity, which implant in the subcapsular and cortical sinusoids and the neovessels that they generate penetrate through the lymph node capsule resulting in peripheral vascularity.

Yang and Metreweli[2] evaluated non-hilar cortical blood flow to have a high PPV for metastasis in the setting of an ipsilateral invasive breast cancer.

In our study, peripheral non-hilar cortical blood flow was seen in 28 patients; all 28 patients on histopathological examination had metastatic lymph nodes.

Mixed Vascular Pattern

It was defined as more than one vascular pattern in a lymph node [Figure 9].

In our study, 4 patients showed mixed vascularity, i.e., both hilar as well as non-hilar cortical (peripheral); of these 3, patients revealed metastasis.

Thus, a total number of patients having non-hilar cortical blood flow were 32 (28 peripheral and 4 mixed) The sensitivity, specificity, PPV, NPV, and diagnostic accuracy to detect nodal metastasis were 79.48%, 95.65%, 96.8%, 73.3%, and 85.48%, respectively.

Flow Impedance

Flow impedance is expressed by the values of RI and PI , these are also used as diagnostic criterion to identify metastasis. Theoretically, low impedance, produced by vasodilatation [Figure 10], is encountered in inflammation while vessel compression by tumor cells leads to increased impedance.

RI

The principle of RI is that, in a lymph node, the high resistance of distal vessels produces a low diastolic flow in the feeding artery increasing the difference between the peak systolic velocity and end diastolic velocity.

We observed that mean RI of metastatic nodes was 0.86 ± 0.14 and that of non-metastatic nodes was 0.66 ± 0.21 ($P < 0.001$). The difference was statisically significant and was found to be useful for differentiating benign and metastatic nodes.

We also found that the cutoff value of 0.7 for RI yielded a high sensitivity of 92.10% but low specificity of 56.52%. However, PPV, NPV, and diagnostic accuracy in detecting nodal metastasis were 78.26%, 81.25%, and 79%, respectively.

Dudea *et al.*[3] found that the cutoff value of 0.7 for RI yielded a sensitivity of 86% and a specificity of 70%.

PI

This is a measure of the variability of blood flow in a vessel. In the present study, the mean PI of metastatic nodes was 2.47 ± 1.26 standard deviation ($P < 0.001$) and that of non-metastatic nodes was 1.52 ± 1.16 ($P < 0.001$). A PI >1.4 was found to diagnose metastatic nodes with a sensitivity of 82.5%, specificity of 65.22%, PPV of 80%, NPV of 68.18%, and a diagnostic accuracy of 75.80%.

Dudea *et al.*[3] found that the cutoff value of 1.4 for PI yielded a sensitivity of 80% and a specificity of 86%.

Thus, we have found that pulsed Doppler spectral waveforms obtained from metastasis-bearing lymph nodes tend to have high RI, high PI, and sharp systolic peaks [Figure 11].

CONCLUSION

High-resolution sonographic and color Doppler examination proved as a valuable primary investigation to identify lymph nodes and has a high PPV in differentiating metastatic from non-metastatic (reactive) lymph nodes.

In our study, it was also found that lymph nodes number ≥3, L/S ratio <1.4, RI >0.7, PI >1.4, and non-hilar cortical blood flow were most reliable parameters for diagnosing metastatic lymph nodes with a diagnostic accuracy of 75.80%, 69.35%, 79%, 72.58%, and 85.48%, respectively [Table 8], in patients with known cases of breast cancer. Axillary staging in these patients is very beneficial as it allows the surgeon to proceed directly to ALND and thus avoid an unnecessary SLNB and its complications. Hence USG and color Doppler of axilla serves an important role in the management of patients with breast cancer.

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